

## Scientific Abstract

This randomized, double-blind, placebo-controlled, dose-escalating clinical study will evaluate the effects of several dose levels of intramuscular pVGL.1(VEGF2) plasmid deoxyribonucleic acid (DNA) versus placebo with respect to safety and efficacy in patients with high-risk critical limb ischemia (CLI). The pVGL.1(VEGF2) plasmid contains the complementary DNA sequence for the vascular endothelial growth factor 2 (VEGF-2) protein, a member of a class of natural growth factors that promote angiogenesis. This study will obtain information regarding the safety, duration of activity, and optimal dose of pVGL.1(VEGF2) for the treatment of CLI.

The primary objectives of this study in adult patients with high-risk CLI (Rutherford Clinical Severity Score greater than or equal to 5) are as follows:

- To evaluate, through dose escalation in defined increments, the safety of intramuscular administration of pVGL.1(VEGF2) versus placebo by assessing the frequency, duration, and severity of adverse events
- To assess the effect of single, defined, increasing doses of pVGL.1(VEGF2) given by direct intramuscular injection into the affected leg when compared with placebo on leg ulcer healing (as assessed by ulcer surface area, time to complete healing, and ulcer score)

The secondary objectives of this study in adult patients with high-risk CLI are as follows:

- To assess the effect and/or duration of effect of single, defined, increasing doses of pVGL.1(VEGF2) given by direct intramuscular injection into the affected leg when compared with placebo on Rutherford Clinical Severity Score, ankle-brachial index (ABI), great-toe index (GTI), resting leg pain (as assessed by frequency of rest pain, pain medication use history, sleeping history, and intensity of rest pain), and the incidence and extent of lower leg amputation or other surgical interventions
- To evaluate the relationship between serum VEGF-2 protein levels and measures of safety and efficacy of pVGL.1(VEGF2)

Key inclusion criteria for patients in this study are CLI as defined by a Rutherford score of 5 or greater, nonhealing ulcers or other evidence of tissue loss in the ischemic leg, an ABI of less than 0.6 or a GTI of less than 0.3, and angiographic evidence of total occlusion in an artery of the affected leg. Key exclusion criteria are as follows: concomitant disease resulting in a life expectancy of less than 1 year; a history of neoplasm, evidence of retinopathy; a history of recent, successful aortic or lower extremity surgery or angioplasty; and presentation as a suitable candidate for surgical or angioplastic revascularization of the affected limb.

This study will include 12 patients who will be enrolled sequentially into 3 dosing cohorts. Each cohort will consist of 4 patients. Within each dosing cohort, patients will be randomized to receive either pVGL.1(VEGF2) or placebo in a 3:1 ratio. Three pVGL.1(VEGF2) dose levels will be used: 2, 4, or 8 mg. The patient will receive the total dose by 8 intramuscular injections into the affected limb given in a single session.

All patients in a dosing cohort will be evaluated for safety prior to progressing to the next dosing cohort; therefore, dosing in successive cohorts will occur not less than 4 weeks apart. The study will consist of a Screening/Baseline Phase (up to 2 weeks before treatment), a Treatment Phase (1 day), and a Post-treatment Phase (12 weeks following treatment). Following completion of this study at 12 weeks, all patients will enter a 12-week safety follow-up study.

An efficacy analysis will be conducted for all patients randomized into the study (*i.e.*, the intent-to-treat population). A secondary analysis for patients who complete the Week 4, 8, and 12 of the Post-treatment Phase assessments will also be performed.